

Nivolumab (BMS-936558)

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee

November 5, 2013



Bristol-Myers Squibb

Agenda

Introduction

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Proposal and Data to Support Nivolumab Pediatric Development Plan

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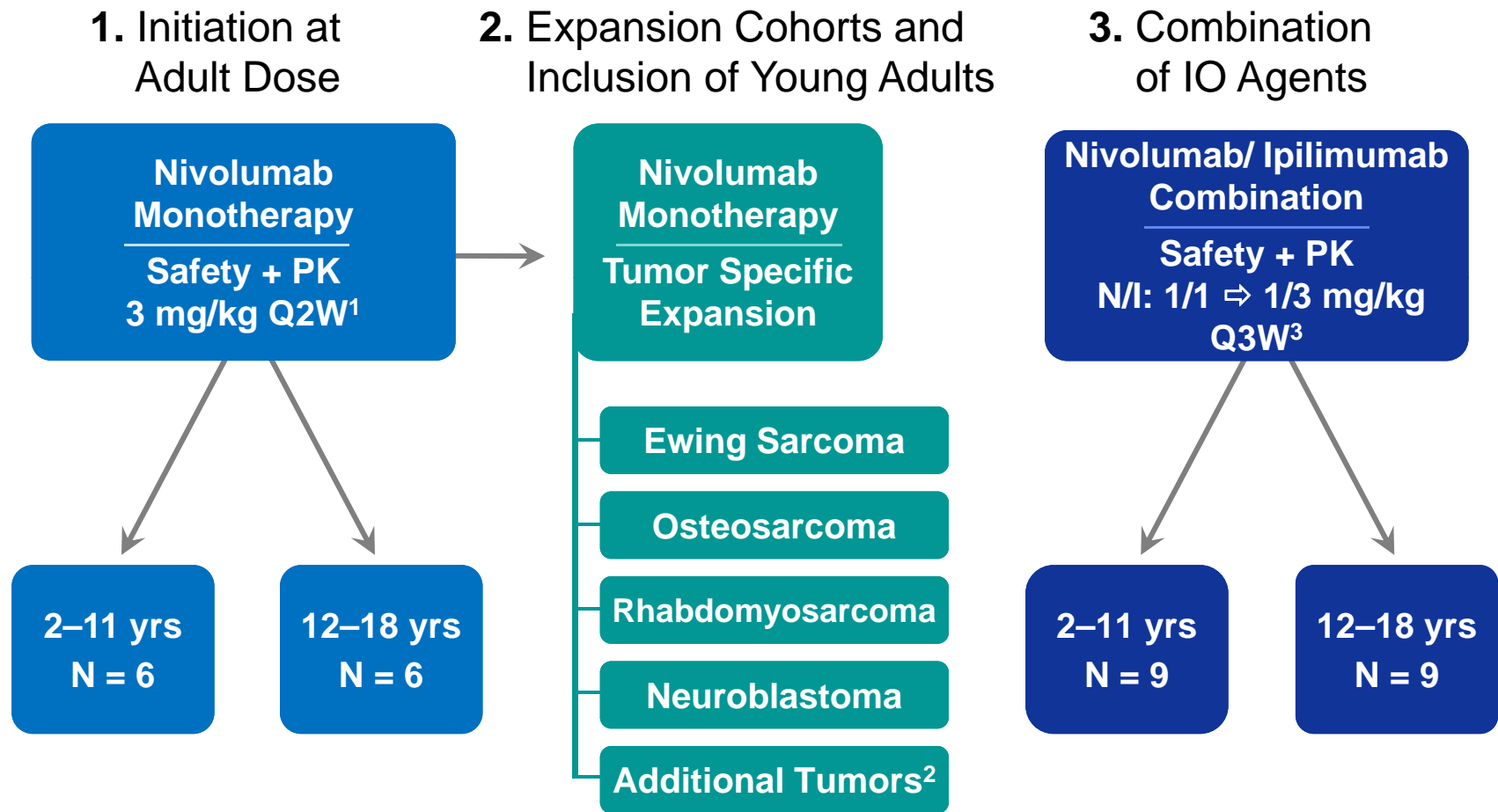
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Addressing Unmet Needs in Pediatric Patients

- ◆ **Goal is a global pediatric program which efficiently and safely evaluates nivolumab in tumors relevant to the proposed population**
- ◆ **Multiple collaborations have led to this innovative proposal**
 - **July 2013: Meeting with FDA and NCI**
 - **September 2013: Meeting with EMA's PDCO**
 - **Multiple consultations with US and EU pediatric experts**

Initial Pediatric Ph1/2 Study Design

Three Elements of Innovation



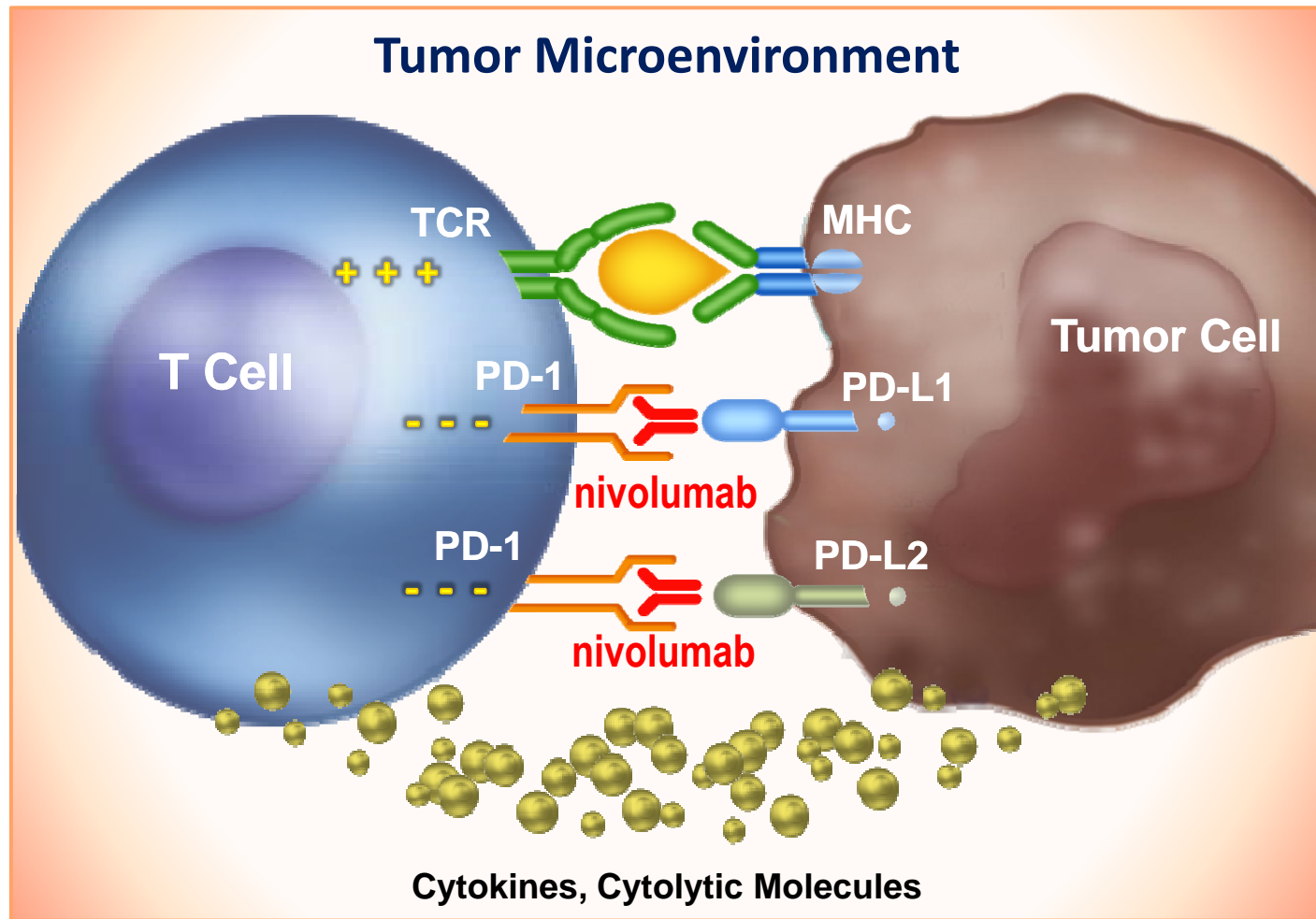
¹Dose de-escalation as needed

²Additional tumor specific cohorts based on biomarker studies, other unmet medical needs, and relevant adult experience.

³Dose escalation

Mechanism of Action for Nivolumab

Nivolumab is a fully human monoclonal IgG4 antibody



Initiation at Adult Dose and Schedule

- ◆ **No evidence of dose-response relationship for safety was observed up to 10 mg/kg in adult patients across multiple tumor types ¹**
- ◆ **The regimen of 3 mg/kg Q2W was chosen for the ongoing Phase 3 program and constitutes our largest experience across the adult program**
- ◆ **Exposure in pediatric patients is expected to be similar to that of adults receiving the same mg/kg dose, as clearance of nivolumab decreases with decrease in body weight ²**
- ◆ **Study investigators support the initiation of pediatric studies at the 3 mg/kg dose and schedule**
- ◆ **Ipilimumab pediatric data support similar safety profile of checkpoint inhibition in pediatric and adult patients**

1. Topalian S., et al., *NEJM* 2012; 366 (26):2443-2454.

2. Agrawal, S., et al. Poster Presentation at ASCO: 2012 June 2-5; Chicago IL: Abstract TPS2622.

Nivolumab Phase Ib in Adults: Treatment-Related Adverse Events in $\geq 1\%$ of All Treated Patients

Event	Nivolumab, Event Percent							
	1 mg/kg (N=79)		3 mg/kg (N=50)		10 mg/kg (N=130)		Total (N=296*)	
	All	Gr 3 or 4	All	Gr 3 or 4	All	Gr 3 or 4	All	Gr 3 or 4
Any AE	49	6	38	4	38	8	41	6
Rash	20	-	8	-	8	-	12	-
Diarrhea	19	-	6	-	9	2	11	1
Pruritus	16	-	8	-	7	1	9	<1
ALT increased	5	-	4	-	3	2	4	1
AST increased	3	-	4	2	2	1	3	1
TSH increased	3	-	4	-	2	1	3	<1
Pneumonitis**	4	3	2	-	4	1	3	1
Infusion-related reaction or hypersensitivity	3	-	6	-	3	1	3	<1
Hypothyroidism	3	-	2	-	2	1	2	<1
Hyperthyroidism	-	-	2	-	1	1	1	<1

* 37 patients treated at the 0.1 and 0.3mg/kg doses

** Grade 3 or 4 drug related pneumonitis developed in 3 patients (1%), leading to death

Nivolumab Phase Ib in Adults: Efficacy Across Broad Range of Tumors

	Nivolumab Dose Level (mg/kg Q2W)				
	0.1	0.3	1	3	10
Objective Response Rate (ORR)					
NSCLC – SQ¹ N=54	--	--	0 (0/15)	22% (4/18)	24% (5/21)
NSCLC – NSQ¹ N=74	--	--	6% (1/18)	26% (5/19)	19% (7/37)
Melanoma² N=107	35% (6/17)	28% (5/18)	31% (11/35)	41% (7/17)	20% (4/20)
RCC³ N=34	--	--	28% (5/18)	--	31% (5/16)

Response evaluation by standard RECIST

8 patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation.

1. Brahmer J, et al. Adapted from a Poster Presentation at ASCO; 2013 June 1-4; Chicago IL: Abstract 8030.

2. Sznol M, et al. Adapted from Oral Presentation at ASCO; 2013 June 1-4; Chicago, IL: Abstract 9006.

3. Drake CG, et al. Adapted from a Poster Presentation at ASCO; 2013 June 1-4; Chicago IL: Abstract 4514.

Proposed Pediatric Trial Expansion Cohorts

- ◆ **Initiate evaluation in select pediatric tumors with unmet medical need**
- ◆ **Possibility to add cohorts according to signals detected in nivolumab program (e.g. CNS tumors)**
- ◆ **Allow inclusion of young adults**

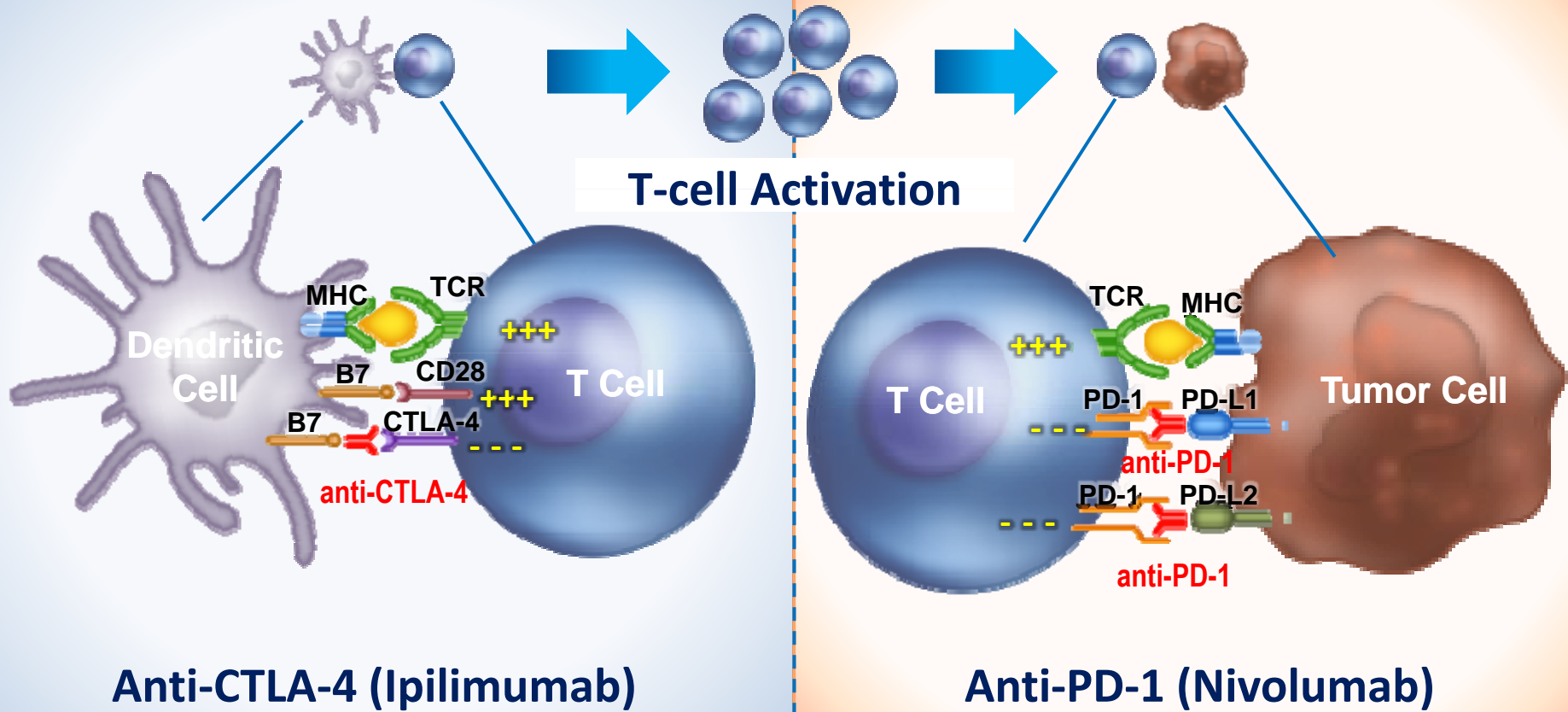
PD-L1 Receptor Ligand as a Biomarker

- ◆ Data suggest that PD-L1 expression on tumor cells may be associated with tumor response^{1,2}
- ◆ PD-L1 expression using the BMS-Dako assay is being evaluated in pediatric tumor tissue in collaboration with US and EU investigators
- ◆ Ongoing phase 3 nivolumab trials in NSCLC, melanoma, and RCC will explore the role of PD-L1 expression in the tumor as a potential predictive biomarker for clinical benefit

1. Topalian S., et al., *NEJM* 2012; 366 (26):2443-54h.

2. Grosso JF., et al. Poster Presentation at ASCO; 2013 June 1-4; Chicago IL: Abstract 3016.

Mechanism of Action of Checkpoint Inhibitors



Interim Results of a Phase I Trial of Ipilimumab in Pediatric Patients: Trial Enrollment

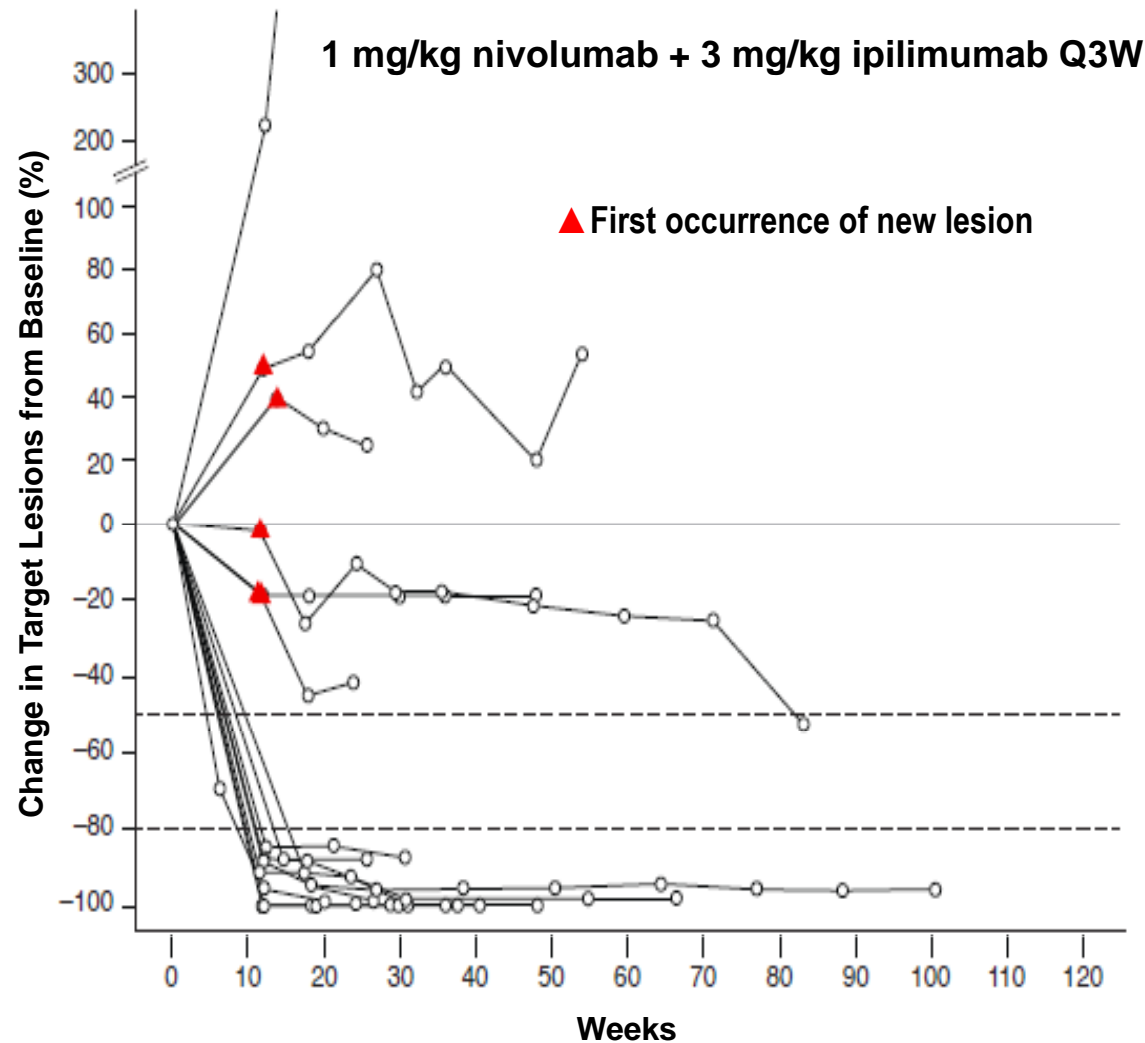
26 patients enrolled, 24 evaluable for toxicity	
Median Age (range)	14 yo (2–21)
Diagnosis of Enrolled Patients	
Metastatic Melanoma	9
Osteosarcoma	7
Synovial Sarcoma	2
Rhabdomyosarcoma	1
Renal Cell Carcinoma	1
Transitional Cell Carcinoma	1
Neuroblastoma	1
Spindle Cell Sarcoma	1
Undifferentiated Sarcoma	1
Clear Cell Sarcoma	2

- Trial accrual initiated September 2008. Currently 3 sites are accruing.

Interim Results of a Phase I Trial of Ipilimumab in Pediatric Patients: Immune Related Adverse Events (irAE)

	Ipilimumab			
	1 mg/kg (N=3)	3 mg/kg (N=3)	5 mg/kg (N=8)	10 mg/kg (N=10)
Grade 1	Colitis Rash	Colitis		
Grade 2			Transaminitis Rash Autoimmune Thyroiditis	Autoimmune Thyroiditis Myalgias
Grade 3			Hypophysitis Transaminitis Angioedema during infusion	Colitis Transaminitis Pleural effusions
Grade 4			Pancreatitis	

Concurrent Nivolumab and Ipilimumab in Adults with Melanoma



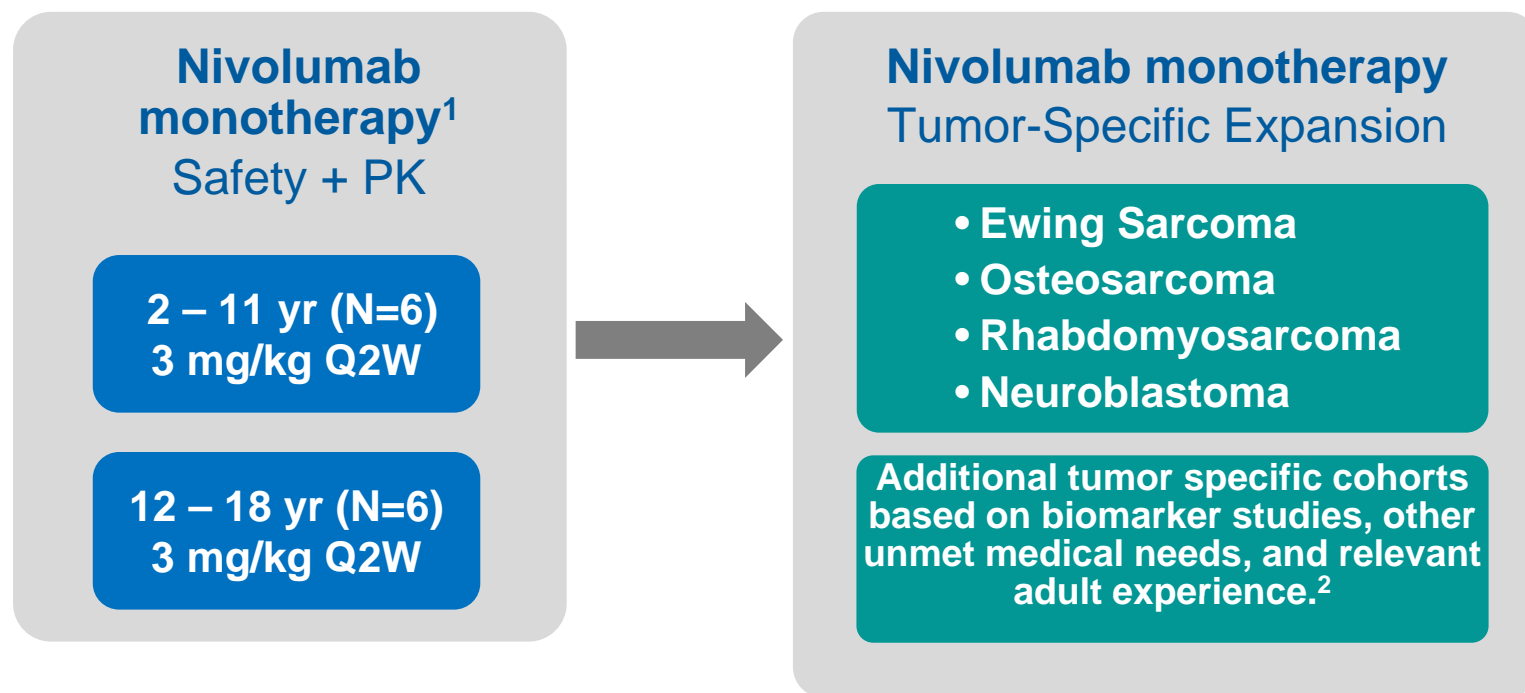
Drug-Related Adverse Events in Adults

Preferred Term	Nivolumab + Ipilimumab ¹ CA209-004 N=53		Ipilimumab ² MDX010-20 N=380	Nivolumab ³ CA209-003 N=296
	Any Grade n (%)	G3-4 n (%)	G3-4 n (%)	G3-4 n (%)
Related AEs	49 (93)	28 (53)	66 (17)	41 (14)
Rash	29 (55)	2 (4)	5 (1)	-
Pruritus	25 (47)	-	1 (<1)	1 (<1)
Diarrhea	18 (34)	3 (6)	14 (4)	3 (1)
AST increased	11 (21)	7 (13)	1 (<1)	2 (1)
ALT increased	11 (21)	6 (11)	2 (<1)	2 (1)
Lipase increased	10 (19)	7 (13)	2 (<1)	2 (1)
Amylase increased	8 (15)	3 (6)	2 (<1)	-
Colitis	5 (9)	2 (4)	12 (3)	-
Pneumonitis	3 (6)	1 (2)	1 (<1)	3 (1)
Uveitis	3 (6)	2 (4)	-	-
Thyroiditis	3 (6)	-	-	-
Hypophysitis	2 (4)	1 (2)	2 (<1)	-
Pancreatitis	2 (4)	1 (2)	-	-
Nephritis	2 (4)	2 (4)	-	-
Adrenal insufficiency	2 (4)	-	2 (<1)	-
Hyperthyroidism	2 (4)	-	-	1 (<1)

^{1,3} Data pooled across all dose cohorts

² MDX010-20 used ipilimumab 3 mg/kg + GP100

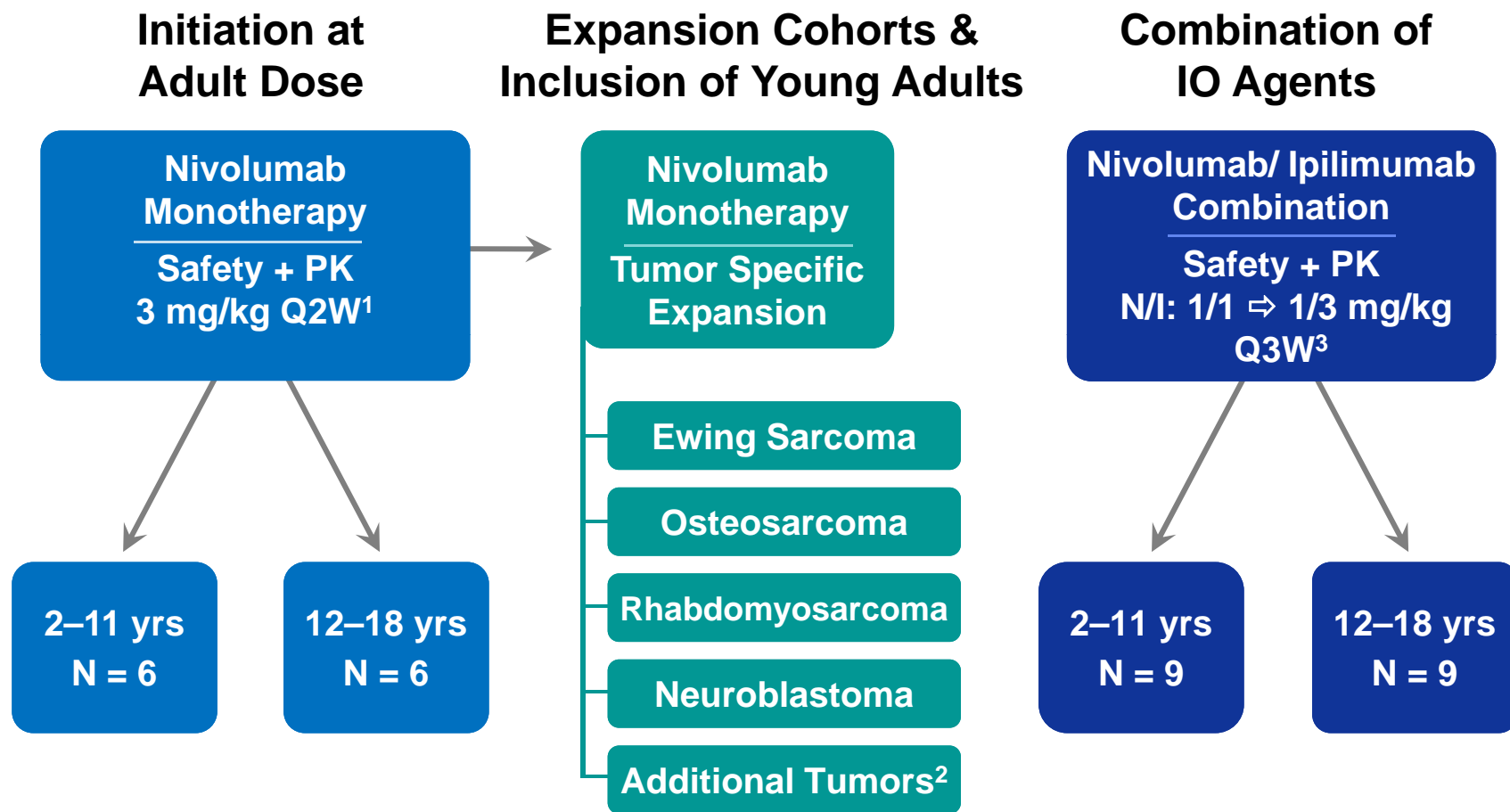
Proposed Pediatric Ph1/2 Study Design: Monotherapy



¹ Dose de-escalation as needed

² Young adults will be entered in the expansion cohorts

Proposed Pediatric Ph1/2 Study Design: Expansion and Combination



¹Dose de-escalation as needed

²Additional tumor specific cohorts based on biomarker studies, other unmet medical needs, and relevant adult experience.

³Dose escalation

Additional Components of the Proposed Global Pediatric Development Plan

- ◆ **Nonclinical biomarker study**
 - **Samples from pediatric tumor banks**
- ◆ **Planned studies addressing PIP requirements:**
 - **Modeling and simulation studies**
- ◆ **Confirmatory efficacy study based on activity signals**

Summary

- ◆ **Goal is to efficiently develop a global pediatric program for nivolumab in tumors relevant to pediatric patients**
- ◆ **Innovative approaches are needed to accelerate pediatric development**
- ◆ **Immuno-Oncology agents provide unique opportunities for collaborative pediatric development with Health Authorities and investigators globally**